The Annals of Clinical and Analytical Medicine
Original Research

Pathologic response prediction and neoadjuvant rectal score evaluation in patients with rectal cancer

Rectal cancer

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Abstract

Aim: In this study, we aimed to evaluate the factors of neoadjuvant chemoradiotherapy (nCRT) affecting the pathologic response in locally advanced rectal cancer. Material and Method: A total of 80 rectal cancer patients undergoing nCRT were included in the study to investigate clinical and pathological factors associated with tumor regression grade. Neoadjuvant rectal scoring (NAR) was calculated to predict overall survival. Results: Thirteen patients (16%) were detected to have pathologic complete response (pCR) and 24 patients (30%) as pathologic poor response (pPR). Tumor size in pCR group was smaller than the in other groups (p=0.003). Distal tumor localization and clinical complete response (cCR) were associated with pCR (p=0.007, p<0.005 respectively). Higher rates of pPR were observed in patients with residual tumours (cPR) (p=0.007). The factors correlated to low NAR were distal tumor localization, pathologically negative lymph nodes, cCR, and pCR (p=0.003, p=0.017, p<0.005, p<0.005 respectively). Statistically significant correlations were identified between high NAR and PET-CT stage III disease (p=0.03), pathologic lymph node metastasis (p<0.005) and cPR (p=0.007). Discussion: Clinical and pathologic factors are correlated with tumour regression grade and 5-year overall survival expectancy. Studies with larger sample sizes are needed to better elucidate these groups of patients and develop more effective treatments.

Keywords

Neoadjuvant Chemoradiotherapy; Neoadjuvant Rectal Scoring; Rectal Cancer; Tumor Regression Grade

DOI: 10.4328/ACAM.6047 Received: 10.10.2018 Accepted: 22.11.2018 Published Online: 27.11.2018 Printed: 01.09.2019 Ann Clin Anal Med 2019;10(5): 581-5
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Introduction

Colorectal cancer is the fourth most common form of cancer worldwide. Rectal cancer represents approximately one-third of all colorectal cancers. More than 90% of all rectal cancers are adenocarcinomas and the primary treatment for a potential curative disease is surgery [1]. Adjuvant therapies should be added following the surgery in patients with risk of local recurrence [2]. Local recurrence significantly decreases with neoadjuvant chemoradiotherapy (nCRT) compared to adjuvant treatment in patients with locally advanced rectal cancer [3].

Locally advanced rectal cancer patients are typically treated by surgery following preoperative chemoradiotherapy [4]. Studies on rectal cancer requires long-term follow-up since recurrence occurs in the late stage following the treatment, and therefore, an early endpoint with well-established prognostic significance would improve the evaluation of the treatment outcomes in the early period [5]. One of the prognostic factors used for this purpose is the Tumour Regression Grade (TRG), in which grading is performed by comparing the level of fibrosis versus the viable tumor cell counts. Absence of viable tumor cells indicates pathological complete response (pCR), while a dominant tumor without fibrosis indicates a mass poor response (pPR). Long-term outcomes were shown to be better in tumors with pCR than in tumors with pPR [5, 6].

Valentini et al. developed a nomogram to predict overall survival by investigating the clinical factors in rectal cancer patients who received nCRT [7]. In the subsequent years, using the clinical factors recommended by the nomogram, the neoadjuvant rectal score (NAR) was developed. NAR is important in predicting overall survival in clinical studies. The survival expectancy decreases as NAR increases [8].

Following nCRT, pPR is the most likely outcome; however, the factors affecting treatment response are not clear. Many studies have investigated pCR-associated factors. The purpose of this study was to investigate the clinical and/or pathological factors that could be used to predict refractory patients with pPR, as well as patients with pCR.

Material and Method

In this study, we included eighty patients with the diagnosis of rectal cancer of clinical stage 2 and 3, who have received nCRT at our clinic between 2013 and 2017. Histopathological diagnosis was confirmed before treatment and pelvic magnetic resonance imaging (MRI) and positron emission tomography (PET-CT) imaging was performed for local regional and distant metastasis staging. In accordance with the American Joint Committee on Cancer (AJCC) seventh edition TNM staging system [9], clinical stage 2 and 3 patients were included. All patients had a performance between 0 and 2 according to the Eastern Cooperative Oncology Group (ECOG) scoring system [10]. Patients with an ECOG score ≥3 and stage 4 disease were excluded. The patient files were analyzed retrospectively and information on age, gender, disease stage, and treatment was obtained. The study was approved by the institutional ethics committee.

Radiotherapy:

Patients were immobilized using a belly board in prone position. Computed tomography (CT) (GE-Light Speed 64, GE, US) images were obtained with a 2.5 mm slice thickness, covering the entire pelvis from the upper abdomen to the bottom of the perineum. With the help of the PET-CT and pelvic MRI images, the primary tumour region was contoured as the gross tumour volume (GTV). The clinical tumour volume-1 (CTV-1) was obtained by adding 20 mm margin in all directions to GTV. CTV-2 contained internal iliac, external iliac and all pre-sacral lymph nodes, in addition to CTV-1. Adding a 5mm margin to CTVs, the planning target volume-1 (PTV-1) and PTV-2 were obtained. The outlined organs at risk (OAR) were the bladder, the bilateral femoral heads, and the small intestine surrounding the PTV-2. For each patient field-in-field (FIF) plan was designed with the CMS-XiO (Elekta®, UK) treatment planning system (TPS). Three-field FIF plans were performed using 18 MV photons. 45 Gy radiotherapy was administered to PTV-2 with 1.8 Gy fraction dose using 5 days weekly standard fractionation, and a 5.4–9 Gy boost was administered to PTV-1 to complete the total dose to 50.4–54 Gy or a total dose of 25 Gy was administered to PTV-2 in 5 fractions of 5 Gy each for 5 consecutive days. All patients continued treatment without any interruptions.

Chemotherapy:

One of the following chemotherapy regimens was administered concomitantly with radiotherapy: capecitabine 825 mg/m2, twice daily, 5 days a week, for 5 weeks or 5FU 225 mg/m2 over 24 hours 5 or 7 days/week or bolus 5FU 400mg/m2 plus bolus leucovorin 20 mg/m2, 4 days during week 1 and week 5 of conventional radiotherapy. Chemotherapy was planned in accordance with patient age and ECOG scoring system.

Surgery:

Patients underwent preoperative colonoscopy and/or MRI assessment and then transabdominal resection was performed. Rectum and the mesorectum, containing the surrounding lymph nodes were extracted with total mesorectal excision. Low anterior resection was performed, leaving a 5 cm margin in the case of proximal tumours and a 2 cm margin in the case of distal tumours. Abdominoperineal resection was performed if a safe 2 cm surgical margin could not be ensured.

Pathology:

A post-operative pathology specimen was investigated by two pathologists. The tumor area was sampled totally and at least 8 sections were taken from each tumor. The grade, depth of invasion (T stage), number of evaluated and positive lymph nodes (N stage), extranodal deposits, proximal, distal and circumferential margins, lymphovascular invasion and perineural invasion were reported. For the assessment of tumor response to nCT, the modified tumor regression grade by Ryan et al. was used [11] (Table 1). The complete absence of a viable tumor, known as pCR, was recorded as grade 0. If pPR was observed in the treatment-refractory tumors, they were recorded as grade 3.

Neoadjuvant rectal score:

The formula below (eq. 1) is used to calculate NAR.

$$NAR = \frac{[5pN \square 3(cT \square pT) + 12]^2}{9.61} \quad (1)$$

Where the pathologic nodal stage (pN) is an element of the set {0, 1, 2}, the clinical tumour stage (cT) is an element of the set {1, 2, 3, 4}, and the pathologic tumour stage (pT) is an element of the set {0, 1, 2, 3, 4}. The results were assessed in 3 groups: low (NAR<8), intermediate (NAR [8–16]) and high (NAR>16).

Statistical Analysis:

SPSS version 21 software (IBM Corp., Armonk, NY, USA) was used for the statistical analyses. Chi-Square test of independence, Kruskal-Wallis H test, and Mann-Whitney U test were performed to analyze the variations for tumor regression grades and also to test the correlation of the related factors. A p-value of <0.05 was considered to be statistically significant.

Table 1. Tumour regression grade

Grade	Description
G0 (Complete response)	No viable cancer cells
G1 (Moderate response)	Only small groups or single cancer cells
G2 (Minimal response)	Residual cancer with predominant fibrosis
G3 (Poor response)	Extensive residual cancer

Table 2. Patient characteristics

	N	%
Gender		
Female	33	41
Male	47	59
Histopathology		
Adenocarcinoma	74	92.5
Mucinous adenocarcinoma	6	7.5
Tumour location		
First 10 cm	47	59
Rectosigmoidal	33	41
MRI stage		
II	33	41
III	47	59
PET-CT stage		
II	27	34
III	53	66
Radiotherapy		
25Gy	2	3
50.4Gy	69	86
54Gy	9	11
Chemotherapy		
None	3	4
Capecitabine	35	44
5FU/LV	24	30
Inf.5FU	18	22
Surgery		
LAR	62	77.5
APR	18	22.5

MRI: Magnetic resonance imaging
PET-CT: Positron emission tomography
LAR: Low anterior resection
APR: Abdominoperineal resection
5FU/LV: Fluorouracil + leucovorin
Inf.5FU: Infusional Fluorouracil

Table 3a. Factors affecting tumour regression grade

	pCR	G1	G2	pPR
Tumour size (cm)	4.6 ± 1.4	6 ± 1.4	6.3 ± 2.1	6.2 ± 2.3
CEA (ng/ml)	10.6 ± 26.6	8.9 ± 14.7	7.1 ± 10.4	8.1 ± 9.9
CA19.9 (U/ml)	10.9 ± 7.5	31.2 ± 70.1	33.3 ± 60.4	63.5 ± 158.7
SUV_{max}	15.5 ± 6.2	15.8 ± 8.1	16.1 ± 8.7	14 ± 4.4

pCR: Pathologic complete response
G1: Pathologic moderate response
G2: Pathologic minimal response
pPR: Pathologic poor response
CEA: Carcinoembryonic antigen
CA19.9: Cancer antigen 19-9
SUV_{max}: Maximum standard uptake volume

Table 3b. Factors affecting tumor regression grade

	Patient (N:80)			
	pCR	G1	G2	pPR
Tumour Localization				
First 10 cm	12	9	15	11
Rectosigmoidal	1	5	14	13
PET-CT stage				
II	6	2	7	12
III	7	12	22	12
Residual Tumour				
(+)	2	12	28	24
(-)	11	2	1	0
Radiotherapy				
25Gy	0	0	1	1
50.4Gy	11	11	27	20
54Gy	2	3	1	3
Chemotherapy				
None	0	0	2	1
Capecitabine	8	4	15	8
5FU/LV	0	5	8	11
Inf.5FU	5	5	4	4
Post-operative T stage				
T0	13	0	0	0
T1	0	6	0	0
T2	0	2	10	7
T3	0	6	15	14
T4	0	0	4	3
Post-operative N stage				
N0	11	11	20	19
N1	2	3	5	2
N2	0	0	4	3
CEA≤5 ng/ml	9	10	19	14

pCR: Pathologic complete response
G1: Pathologic moderate response
G2: Pathologic minimal response
pPR: Pathologic poor response
CEA: Carcinoembryonic antigen
PET-CT: Positron emission tomography
5FU/LV: Fluorouracil + leucovorin
Inf.5FU: Infusional Fluorouracil

Results

Patient characteristics are presented in Table 2. Patient mean age was 59 (22–85) and the female to male ratio was 1:1.4. Thirteen patients (16%) were detected to have pCR, 14 patients (18%) as a moderate response (G1) and 29 patients (36%) as a minimal response (G2). Twenty-four patients (30%) had pPR. Factors affecting tumour regression grade are summarized in Table 3a and 3b.

The mean size of the tumour detected was 5.9 ± 2 cm. Tumour size in pCR group was smaller than the in other groups (p=0.003). In tumors located on the first 10 cm from the anal verge, 12patients (26%) had pCR and 11 patients (23%) had pPR. A statistically significant higher rate of pCR (92%) was observed in distal tumours relative to those located proximally

(p=0.007). Fifty-four percent of 24 pPR tumors were located proximally, and no significant correlation was identified between tumor location and nCRT resistance (p=0.12).

The mean values of CEA and CA-19.9 levels at diagnosis were 8.3 ± 14.6b ng/ml and 38.3 ± 98.9 U/ml, respectively. No statistically significant correlation could be demonstrated between CA-19.9 levels, CEA levels, CEA≤5 ng/ml and tumor regression grade (p=0.4, p=0.1, and p=0.8 respectively).

The maximum standard uptake volume (SUVmax) of the primary tumor, measured with PET-CT, was 15.3 ± 7.1 on average. No statistically significant correlations were detected between PET-CT stage, SUVmax values and tumour regression grade (p=0.063 and p=0.95 respectively).

The preoperative imaging results (colonoscopic or radiologic) following neoadjuvant therapy revealed that 14 patients (17%) had a clinical complete response and 66 patients (83%) had a residual tumor. pCR was observed in 11 of the 14 patients (%79) with clinical complete response (p<0.005). Thirty-six percent (n=24) of the patients with residual tumour had pPR (p=0.007).

Pathological TNM staging was conducted by evaluating the postoperative surgical specimens (AJCC, 7thed). Evaluation revealed the following: pT0 in 13 patients (16%), pT1 in 6 patients (7%), pT2 in 19 patients (24%), pT3 in 35 patients (44%) and pT4 tumour in 7 patients (9%). Statistically significant correlation was identified between T stage and tumor regression grade (p<0.005). Sixty-one patients (76%) were pN0, while 12 patients (15%) had pN1 and 7 (9%) had pN2 disease. No statistically significant correlation could be demonstrated between N stage and tumor regression grade (p=0.5).

All of the patients in pCR group were treated with capecitabine and infusional 5FU, however, no significant correlations could be demonstrated between chemotherapy regimens, RT administrations and tumor regression grade (p=0.1 and p=0.6 respectively).

The factors effective on NAR are summarized in Table 4. The correlation between PET stage III disease, the presence of residual tumour, pN+ and high NAR was considered statistically significant (p=0.03, p=0.007 and p<0.005 respectively). None of the patients, in whom pCR was obtained, were in the high NAR group (p=0.01). No significant correlation was identified between high NAR and pPR (p=0.6). The factors that were significantly correlated to low NAR were distal tumour localization, pN-, complete clinical response and pCR (p=0.003, p=0.017, p<0.005, p<0.005 respectively).

Table 4. Factors affecting NAR

	Patients (N:80)		
	NAR <8	8 – 16	NAR >16
	21	35	24
Tumour Localization			
First 10 cm	18	16	13
Rectosigmoidal	3	19	11
PET-CT stage			
II	10	13	4
III	11	22	20
Residual Tumour			
(+)	12	30	24
(-)	9	5	0
Post-operative T stage			
T0	11	2	0
T1	2	4	0
T2	7	10	2
T3	1	18	16
T4	0	1	6
Post-operative N stage			
N0	20	33	8
N1	1	2	9
N2	0	0	7
Tumour regression grade			
pCR	11	2	0
G1	3	8	3
G2	5	11	13
pPR	2	14	8

pCR: Pathologic complete response
G1: Pathologic Moderate response
G2: Pathologic Minimal response
pPR: Pathologic poor response
NAR: Neoadjuvant rectal score
PET-CT: Positron emission tomography

Discussion

The treatment response differs among patients with locally advanced rectal cancer receiving neoadjuvant chemoradiotherapy. A pathologic complete response is obtained in only 10–30% of the patients. In other patients, treatment response occurs as tumour regression or lack of response [5,6]. In our study, among the patients who received nCRT, pCR was obtained in 16% (n=13) of the 80 patients and pPR was obtained in 30% of the patients (n=24). The number of patients with no treatment response was 1.8-fold higher than those with complete response. Many studies have previously investigated pCR. However, to the best of our knowledge, no prospective randomized studies have been published on pPR and the factors affecting pPR.

In a retrospective study by Kalady et al [12], 242 patients were grouped as pCR and non-pCR. A time period longer than 8 weeks between radiotherapy and surgery was reported to be factors that affected pCR. Das et al. [13] evaluated 562 patients and detected that a tumor circumferential extending >60% and CEA >2.5 ng/ml were associated with low pCR. Zeng et al. in their study [14], investigated 323 patients in 2 groups with and without pCR. CEA≤5 ng/ml was reported to significantly increase the pCR rate. Whereas in our study, we investigated the complete and poor response groups based on the pathological tumor regression grade, no correlation could be demonstrated between CEA ≤5 ng/ml and pathologic response (p=0.8).

Garland et al [15] investigated pCR-associated clinical factors in 297 patients. A smaller tumor size and pre-treatment nodal stage were described as independent predictors of obtaining pCR. In our study, the mean size of tumour detected were 4.6 ± 1.4 cm in pCR patients and 6.5 ± 2.1 cm in pPR patients. Tumour size in pCR group was smaller than in the other groups (p=0.003). Another factors that affected pCR were distal tumor localization and clinical complete response while the only factor affecting pPR included the presence of residual tumour (p=0.007, p<0.005 and p=0.007, respectively). There was no statistically significant correlation between tumour localization and residual tumour (p=0.12).

Using the nomogram developed by Valentini et al., overall survival could be predicted by investigating the clinical factors in rectal cancer patients who have received neoadjuvant chemo-

therapy [7]. Using the neoadjuvant rectal score (NAR) developed using the clinical factors recommended by the nomogram, for patient data from the NSABP R-04 study [8], a statistically significant correlation between NAR and overall survival (p<0.001) was detected. In the NSABP R04 study, grouping patients into 3 groups as low (NAR<8), intermediate (NAR=8–16) and high (NAR>16), the 5-year survivals were 92%, 89% and 68% respectively (p<0.0001). In the CAO/ARO/AIO-94 (Working Group of Surgical Oncology/Radiation Oncology/Medical Oncology of the German Cancer Society) study [16], the 10-year survival was reported to be 89.5% in patients with pCR and 39.6% in those with pPR.

In a retrospective study performed by Roy et al. [17], they assessed the utility of pCR and the NAR scoring system to predict disease-free survival (DFS) and overall survival for rectal cancer patients undergoing nCRT. The researchers reported that pCR and lower NAR scores were both associated with significantly longer DFS (p=0.002, p<0.0001 respectively) and overall survival at 5 years (p=0.002, p<0.0001 respectively).

Recently, Fokas et al. [18] investigated the NAR score as a surrogate for DFS in patients with rectal carcinoma treated in the CAO/ARO/AIO-04 randomized phase 3 trial. The results indicated that the NAR score was an independent prognostic factor for DFS and could be used as the primary endpoint in early phase trials.

The limitations of our study included the small sample size and the short follow-up. Therefore, no survival data could be achieved. The assessment we made based on NAR values revealed that all but 2 patient with pCR were in the low NAR group (p<0.005). No similar association was detected between pPR and high NAR (p=0.6). Due to its statistically significant correlation to high NAR, our survival expectancy would be low in cases of PET-CT stage 3 disease, the presence of residual tumour and pN+ disease.

Following neoadjuvant chemoradiotherapy, tumor localization, PET-CT stage, clinical tumor response, pathologic lymph node status and tumor regression grade can be used as independent clinical predictors of 5-year overall survival expectancy. Small tumor size and distal localization of tumour can be predictors of pathologic complete response. Poor treatment response can be obtained in a statistically significant portion of patients with residual tumor. Studies with a larger sample size are needed to elucidate these patient groups.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:
Duman E, Yıldırım Ş. Pathologic response prediction and neoadjuvant rectal score evaluation in patients with rectal cancer. Ann Clin Anal Med 2019;10(5): 581-5.